Longitudinal adverse event assessment in oncology clinical trials: the Toxicity over Time (ToxT) analysis of Alliance trials NCCTG N9741 and 979254

Gita Thanarajasingam, Pamela J Atherton, Paul J Novotny, Charles L Loprinzi, Jeff A Sloan, Axel Grothey

Summary

Background Traditional methods of reporting adverse events in clinical trials are inadequate for modern cancer treatments with chronic administration. Conventional analysis and display of maximum grade adverse events do not capture toxicity profiles that evolve over time or longer lasting, lower grade toxic effects; we aimed to address this shortcoming in this study.

Methods We developed an analytic approach and standardised, comprehensive format, the Toxicity over Time (ToxT) approach, which combines graphs and adverse event tabular displays with multiple longitudinal statistical techniques into a readily applicable method to study toxic effects. Plots visualising summary statistics or individual patient data over discrete timepoints were combined with statistical methods including the following longitudinal techniques: repeated measures models that describe the changes in adverse events across all cycles of treatment; time-to-event analyses of first and worst grade toxicity; and area under the curve (AUC) analyses summarising adverse event profiles over the entire course of a study, including chronic low-grade events. We applied ToxT analysis to adverse event data from two completed North Central Cancer Treatment Group (NCCTG/Alliance) trials: N9741 (NCT00003594), in which different combinations of oxaliplatin, 5-fluorouracil, and irinotecan were investigated for metastatic colorectal cancer, and 979254, in which survivors of breast cancer were given venlafaxine or placebo for control of hot flashes.

Findings In trial NCCTG 979254 there was a higher incidence of late-occurring dry mouth in patients who were given venlafaxine than in those given placebo (week 1 [baseline]: 13% [six incidence in 48 patients, SD 5] *vs* 22% [11/49, SD 6]; p=0·20; week 5: 49% [24/49, 7] *vs* 2% [1/46, 2]; p<0·0001). In trial NCCTG N9741 there was an increased incidence of early nausea for patients given irinotecan plus oxaliplatin (IROX) compared with those given 5-fluorouracil plus oxaliplatin (FOLFOX; cycle 1 mean grade nausea 1·1 [SD 1·0] *vs* 0·6 [0·7]; p<0·0001). Event charts showed earlier occurrences of higher grades of diarrhoea for patients given IROX compared with those given FOLFOX, and the AUC analysis shows a higher magnitude of diarrhoea consistently over time throughout the study in patients given IROX versus those given FOLFOX (mean AUC 4·2 [SD 5·2] *vs* 2·9 [4·2]; p<0·0001).

Interpretation The ToxT analytical approach incorporates the dimension of time into adverse event assessment and offers a more comprehensive depiction of toxic effects than present methods. With new, continuously administered targeted agents, immunotherapy, and maintenance regimens, these improved longitudinal analyses are directly relevant to patients and are crucial in cancer clinical trials.

Funding National Cancer Institute of the National Institutes of Health and the Mayo Comprehensive Cancer Center.

Lancet Oncol 2016; 17: 663–70

Published Online
April 12, 2016
http://dx.doi.org/10.1016/S1470-2045(16)00038-3

See Comment page 553

Division of Hematology (G Thanarajasingam MD), **Division of Medical Oncology** (Prof C L Loprinzi MD, Prof A Grothey MD), **and Alliance Statistics and Data Center** (P J Atherton MS, P J Novotny MS, Prof J A Sloan PhD), **Mayo Clinic, Rochester, MN, USA**

Correspondence to:
Dr Gita Thanarajasingam, Division of Hematology, Mayo Clinic, Rochester, MN 55905, USA
thanarajasingam.gita@mayo.edu

Introduction

A consensus system for reporting of adverse events is a cornerstone of clinical trials in oncology. Precise, complete, and unbiased reporting of adverse events is needed to ensure the safety and tolerability of novel agents or combinations in trials of cancer treatments. Characterisation of adverse events is also important to patients and clinicians engaged in shared decision making about a treatment strategy. Several initiatives have tried to improve the quality of harms-related data reporting and to standardise the reporting of toxic effects.[1–4] However, little attention has been paid to the modernisation of methods of toxicity analysis so that they are consistent with contemporary cancer treatments and trials.

During the past decade, the rapid expansion of novel, individualised treatments against cancer has driven a change in the complexity of clinical trials investigating these drugs. Newer agents, such as targeted treatments and immunotherapy, are sometimes used continuously over months or years, rather than for a set number of cycles. Maintenance regimens are increasingly relevant in various settings, from multiple myeloma post-transplant to metastatic colorectal cancer. Moreover, improvements in supportive care have made possible extended durations of treatment. The consensus method for reporting adverse events has not evolved in parallel with extended treatment durations.

Many limitations are associated with methods for capturing and displaying adverse event data. Tables of

Research in context

Evidence before this study

Conventional reporting of toxic effects in cancer trials is inadequate in the era of chronically administered, novel cancer treatments. The traditional maximum grade approach to reporting toxic effects does not depict onset, duration, or trajectory of adverse events, nor does it address longer lasting, lower grade toxic effects that might occur at substantial expense to a patient's quality of life. A narrow focus on high-grade toxic effects is insufficient and potentially misleading.

Longitudinal and graphical methods of assessing adverse events exist, but to our knowledge, there have not been any clinically focused efforts specifically aimed at modernising the approach to adverse event evaluation to better show the side-effects of newer, chronic treatments for cancer. We aimed to challenge conventional methods of adverse event reporting and present a novel approach to toxicity analysis that assesses adverse events over time.

Added value of this study

Using adverse event data from two completed trials, our findings show that the Toxicity over Time (ToxT) method can be used to construct clinically meaningful statistical summaries of adverse event data over time. The various outputs recorded in the ToxT analysis uncover clinically relevant information such as time to onset of adverse events and the potential to identify subpopulations of patients with atypical adverse event responses.

Implications of all the available evidence

Our study demonstrates a practical application of a new, longitudinal approach to adverse event analysis. An improved, clinically oriented, longitudinal approach adverse event analysis fulfils an important and unmet need in oncology. ToxT has a role in the clinic, for optimally counselling individual patients on the anticipated side-effects of a given treatment, and in clinical trials, to better depict adverse events of novel agents or combinations, and to make trials more patient-centred. This type of information might also be central to the process of securing regulatory approval for novel agents in the future.

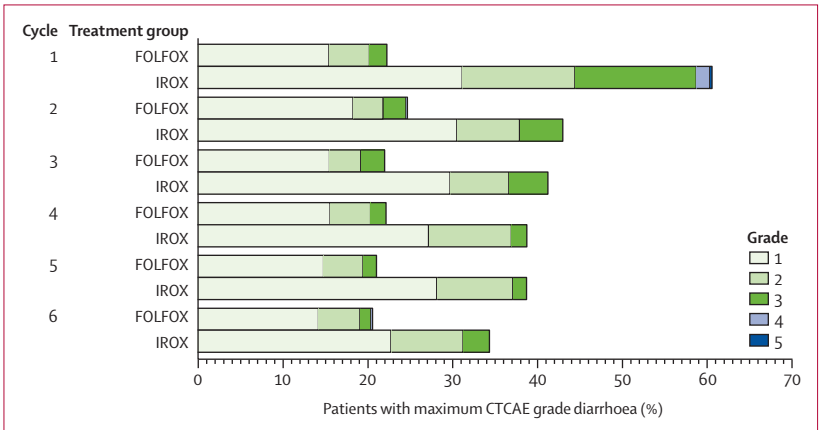

Figure 1: **Incidence of diarrhoea in patients given FOLFOX and IROX in NCCTG N9741 by drug cycle and adverse event grade**

FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. CTCAE=Common Terminology Criteria for Adverse Events.

high-grade events as defined by the Common Terminology Criteria for Adverse Events (CTCAE)[5] traditionally show maximum-grade events experienced during the entire trial. These analyses do not define important information about when an adverse event arose, its duration, or its severity at a given point during treatment.[6] Importantly, conventional methods do not account for longer lasting, lower grade toxic effects that might have substantial ramifications on quality of life. For example, an isolated episode of high-grade diarrhoea, whether or not causally associated with a study drug, is recorded, but chronic grade 2 diarrhoea happening every day over months at a substantial expense to a patient's quality of life is not part of the toxicity assessment.

Inclusion of time-related information would provide a more comprehensive depiction of adverse events that evolve over time. Alternative methods of longitudinal and graphical adverse event evaluation do exist.[7–11] Some propose unique methods of summarising adverse events including bar charts and stream plots,[12] but they do not focus on the comprehensive identification of patterns and differences in toxic effects over time. Importantly, previous approaches have not been applied in an intuitive, clinically oriented format and have not been used for assessment by regulatory agencies. We developed an analytic approach and standardised, comprehensive format, ToxT, which combines graphs and adverse event tabular displays with multiple longitudinal statistical techniques into a readily applicable method to study toxic effects. Here, we applied ToxT analysis to data from two completed cancer clinical trials to exemplify its use for depicting adverse event profiles over time.

Methods

Study design

We used adverse event data from two completed North Central Cancer Treatment Group (NCCTG/Alliance) trials to show multiple longitudinal analyses that constitute the ToxT tool. NCCTG is now part of the Alliance for Clinical Trials in Oncology. N9741 (NCT00003594) was a randomised phase 3 trial of combinations of oxaliplatin, fluorouracil, and irinotecan as initial treatment of metastatic colorectal cancer.[13] 795 patients were randomly assigned to three treatment groups: we used data from the